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Pharmaceutical Preparation

Pharmaceutical preparations wherein an active substance is present bound to a carrier are known in the state of the art in great abundance. In the widest sense, the bond to the carrier can be understood to be purely mechanical; in a narrow sense, however, one makes use of the capacity of carrier substances to enter into special chemical or physicochemical interactions with the active substance or substances.

One category of such interactions are ionic attractive forces, which of course can only be made use of if active agent and carrier are at least partially present in a charged state. In pharmaceutical preparations, ionic bonds between active substances and carriers are used, inter alia, to preserve sparingly soluble active substances which have a low tendency of dissociation in water in their charged and molecular-disperse state, thereby obtaining a high dissolution rate. Apart from this, active agents are bonded to oppositely charged carrier polymers to enable a high active substance load of the preparation; this formulation technique is frequently used, for instance, in liposome preparations. A further variant which has been described are preparations wherein by way of the ionic bond to a charged polymer it is intended to achieve a controlled release of active substance. An example for this is the cough mixture marketed in Germany under the mark Codipront® which contains as active substance carrier complex an active substance base, Codeine poly(styrene, divinyl benzene)sulfonate, bonded to an acidic ion exchanger.

A special form of active ag nts bound to oppositely charged carriers are the so-called nanosols with gelatine or

collagen hydrolysat s as carriers, which are describ d by th firm of Alfatec-Pharma GmbH in various pat nts and published applications, e.g., in the documents DE 41 40 195, DE 41 40 178 and DE 41 40 179. Here, one makes use of the fact that it is easily possible to achieve the desired, isoionic state with charge equalization between carrier and active substance if gelatine or gelatine derivatives are used, thanks to the zwitterionic nature of the same, by means of a corresponding pH adjustment in the preparation. It is described that these nanosols can be used to advantage for the production of medicinal preparations both with rapid and with controlled active substance release.

However, these preparations have the disadvantage that the population has been uncertain for several years as to the possible risks of BSE infection and has increasingly been avoiding products containing gelatine, for example. Therefore, there is a need for preparations without gelatine or collagen derivatives which have the same advantages as, for example, the gelatine-based nanosols described.

It is thus the object of the present invention to provide a pharmaceutical preparation without gelatine or the like, for charged active substances, in which the active substance is present bonded to an oppositely charged carrier.

The object is achieved by a pharmaceutical preparation according to Claim 1.

It was surprisingly found that using chitosans as carriers it is possible to produce so-called nanosols wherein the active substance is present stabilized in a state almost isoionic with the carrier, and that these nanosols are highly suitable for the production of medicinal products.

The preparation of the present invention contains according to Claim 1 at least one pharmaceutical active substance, which is at least partially present in a charged state, i.e. the active substance is capable of forming an ionic state and at least part of the active substance molecules are present in that ionic state.

For a definition of a nanosol, reference is made to DE 41 40 195.

Considered as chitosan derivatives in the spirit of the invention are all modified and unmodified deacetylation products of chitin which still possess a polyglucosamine base structure. The charge opposite to that of the active substance, which is demanded according to the present invention, refers to the net-charge of the carrier used. Thus there may also be charges in the chitosan derivative that are like that of the active substance as long as they are overcompensated by the opposite charges.

In fact, in one of the preferred embodiments there is an active substance with a positive charge that is bonded in the nanosol to a chitosan derivative with negative total charge. Such a chitosan derivative may, for example, be a zwitterionic, partially sulfated chitosan.

In a further, also preferred, embodiment, the active substance is present in a negatively charged state and is bound in the nanosol to a positively charged chitosan derivative, i.e. in the most simple case to an unmodified chitosan. Here, too, an active substance may well be present in a partially undissociated form and may even possess some charges that are like that of the chitosan derivative as long as its net-charge is opposite, i.e. in this case negative.

Preferably, the active substance is present in the nanosol in a colloidal or nanoparticulate distribution, i.e. with an average particle size of at maximum about 500-1000 nm, as far as it is possible to detect a phase boundary between active substance and carrier phase at all. In particular, poorly soluble active agents can be incorporated in this way in pharmaceutical preparations from which they can be quickly released.

The preparations according to the present invention will as a rule contain further auxiliary agents which are commonly used in the pharmaceutics technology and are known to those skilled in the art. These active auxiliary agents may, for example, be further polymeric or non-polymeric carrier substances, but also stabilisers, surfactants, disintegration promoters, antioxidants, dyes, pigments, flavours, sweeteners or other taste-improving agents, binders, lubricants etc. In a preferred embodiment, the preparation contains a further polymeric carrier substance. This can be required, for example, in order to increase the loadability of the nanosol with active substance or in order to modify the release properties of the preparation. Appropriate formulation techniques are likewise known to those skilled in the art.

In accordance with the invention, the herein disclosed pharmaceutical preparations are used for making medicinal products or diagnostic agents. A preferred use of the preparation consists in the production of medicinal agents which are administered as capsules, tablets, powders or granulates, or, like instant preparations, are first dissolved or redispersed in water or another suitable liquid prior to b ing administ red.

In a further preferred embodiment, the preparations are used for preparing medicinal products having controlled active substance release. To this end, they must generally be further modified, i.e. mixed with further auxiliary substances or enclosed by these. For instance, capsules or tablets containing a preparation according to the present invention can be coated with a polymeric film which controls the release of the active agent or agents. These and further techniques for producing medicinal products with modified or controlled release of active substance are known to those skilled in the art.

A preparation according to the present invention is basically produced in a multi-step process which can be varied if necessary or complemented by further steps. Initially, a chitosan derivative is selected as carrier, taking into account the relative number and type of the charged groups of the active agent, which on account of the type and relative number of its charged groups is matched with the active substance in such a way that at a certain pH value an isoionic state or charge equalization can be achieved between active substance and carrier. This is generally the case if the net-charges of active substance and chitosan derivative are opposite and the calculated isoionic point is in a pH range that is physiologically acceptable and is not detrimental to the stability of the active substance.

In a further step, a colloidal aqueous solution is prepared from the chitosan derivative and the active substance, which on account of its polymer content and the viscosity resulting therefrom is a sol. It is of no importance here whether the active substance is added following or prior to dissolving the chitosan derivative, or whether a solution of the chitosan derivative and an indep nd ntly prepared solution of the active substance are united.

In a further step, the pH of the aqueous sol is adjusted such that an isoionic state results. In the course of this pH shift a precipitation of the active substance may occur. It has turned out here that the particles do generally not exceed the colloidal or nanoparticulate size range.

The sol which has been thus prepared and adjusted to an isoionic state can be dried in a further process step. For this purpose, conventional drying methods, but preferably drying methods applying no or only little heat such as freeze drying, may be used.